REMARKS

Claims 2-34 remain pending in the instant application. Claims 18-34 are withdrawn from consideration as drawn to a non-elected invention. Accordingly, claims 2-17 remain under consideration in the instant application.

Support for the claim amendments can be found throughout the claims and specification as originally filed. No new matter has been added. Applicants reserve the right to prosecute the claims as originally filed in this or a continuing application.

Claims 18-34 (Group II) are related to claims 1-17 (Group I) as product and process of use. It is Applicant's understanding that, once the pending product claims are found allowable, any non-elected process claims (Group II, claims 18-34) will be rejoined and examined if such process claims include all of the limitations of the elected product claims (MPEP §821.04).

Acknowledgement of the Withdrawal of Previous Rejections

Applicants gratefully acknowledge the withdrawal of the previous rejection of claims 3-17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Rejection of Claims 2-8 and 10-17 under 35 USC § 103(a)

The Examiner has maintained the rejection of claims 2-8 and 10-17 under 35 U.S.C. §103(a) as being obvious over Ecker *et al.* (US Patent No. 5,965,722) in view of Hojo *et al.* (Eur. Respir. J. 1998), Hammond *et al.* (Nature Reviews Genetics 2001), Bass *et al.* (Nature 2001) and Tuschl *et al.* (WO 02/44321) for the reasons of record set forth in the Office Action mailed April 2, 2007.

The Examiner relies on the cited references for the reasons as summarized in Applicants' Response filed October 2, 2007. Briefly, the Examiner relies on the primary reference, Ecker *et al.*, for teaching that "antisense compounds comprising modified nucleotide bases increase the affinity for base mismatches in mutated genes and further enhance the compounds selectivity for such mutated genes." The Examiner further relies on Ecker *et al.* for teaching that "a single nucleotide mutation is responsible for mutated Ras protein expression," and that "incorporation

of a 2,6-diamino adenosine complementary to the uracil of the mutated codon was also found to be effective in increasing the hybridization of the antisense compound to the mutated gene." The Examiner acknowledges that Ecker *et al.* "do not teach ***siRNA*** targeted to a mutated gene and do not teach ***the point mutation is an adenine or thymine***" (emphasis added).

The Examiner further relies on Hammond *et al.* and Bass et al. for teaching the superior efficacy of RNAi. The Examiner further relies on Hojo *et al.* for teaching that point mutations of the p53 gene are commonly an adenine or a thymidine. Finally, the Examiner further relies on Tuschl *et al.* for teaching that "siRNA may contain at least one modified analogue, such as... 5-bromouracil or 5-iodouracil, and the modification may be located at positions that do not interfere with RNAi mediating activity."

The Examiner alleges that "Ecker *et al.* provide evidence that one of skill in the art would have had a reasonable expectation of inhibiting a mutant target gene," and "given that Tuschl *et al.* teach how to make and use any siRNA targeted to any gene, [and that] Hammond *et al.* and Bass *et al.* teach siRNA are preferred over antisense compounds, one would have had a reasonable expectation of success at making a siRNA targeted to a mutated gene." The Examiner concludes that "the invention would have been prima facie obvious to one of skill in the art."

The test for *prima facie* obviousness is consistent with the legal principles enunciated in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). *Takeda Chem. Indus., Ltd. v. Alpharma Pty., Ltd.*, 2007 U.S. App. LEXIS 15349, at *13 (Fed. Cir. 2007). "While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test, the Court acknowledged the importance of identifying 'a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Id.* at *13-14 (quoting *KSR*, 127 S. Ct. at 1731) (emphasis added). Although the TSM test should not be applied in a rigid manner, it can provide helpful insight to an obviousness inquiry. *KSR*, 127 S. Ct. at 1731. The *KSR* Court upheld the secondary considerations of non-obviounsess, noting that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.*

Applicants respectfully traverse this rejection at least for the reasons set forth in Applicants' response filed October 2, 2007, which are reiterated below. Applicants maintain

that the cited references, alone and in combination, fail to teach or suggest each and every element of the present invention as recited in the claims amended herein.

Claim 2 (and the claims that depend therefrom) is directed to an ***siRNA*** capable of single nucleotide discrimination between a first and second allele, the first allele having 1, 2, 3 or more point mutations relative to the second allele, wherein the siRNA comprises a sense strand and an antisense strand, wherein the antisense strand comprises a ***modified base positioned opposite at least one point mutation in the first allele***, and wherein the modified base is capable of enhancing binding interactions between the siRNA and mRNA encoded by the first allele when compared with binding interactions between the siRNA and mRNA encoded by the second allele. Claim 3 (and the claims that depend therefrom) is drawn to an ***siRNA*** comprising a sense strand and an antisense strand, wherein the sense strand comprises a sequence homologous to a region of a mutant allele encoding a gain-of-function mutant protein, said region comprising one or more point mutations, and wherein the ***antisense strand comprises a sequence comprising one or more modified bases positioned opposite the point mutations***, such that the ***siRNA directs allele-specific cleavage*** of a mRNA encoded by the mutant allele.

The teachings of Ecker *et al.* are directed to ***antisense DNA oligonucleotides*** for specific inhibition of expression of a mutant form of the ras gene. In particular, Ecker *et al.* teach that antisense phosphorothioate DNA oligononucleotides in which 2,6-(diamino)adenine) is positioned complementary to the uracil of the mutated codon 12 of activated ras stabilizes hybridization of the modified antisense oligonucleotide to the activated ras gene and increase specificity for the mutant target. Ecker *et al.* fail to teach or suggest ***any RNA oligonucleotide***, let alone an ***siRNA capable of single nucleotide discrimination***, wherein the antisense strand comprises a ***modified base positioned opposite at least one point mutation in a mutant allele.*** Ecker *et al.* also fail to teach or suggest an siRNA capable of single nucleotide discrimination, wherein the antisense strand comprises ***5-bromo-uridine or 5-iodo-uridine positioned opposite a point mutation of adenine*** in a mutant allele, as required by claim 6. Ecker *et al.* also fail to teach or suggest an siRNA capable of single nucleotide discrimination, wherein the antisense strand comprises ***2,6-diaminopurine positioned opposite a point mutation of thymine*** in a mutant allele, as required by claim 8.

One skilled in the art would not have had the motivation to extend the teachings of Ecker *et al.* to siRNA molecules, since nothing in the teachings of Ecker *et al.* suggests a need in the

art for an alternate molecule to an antisense molecule for the specific inhibition of expression of a mutant gene. Moreover, Ecker *et al.* ***teach away*** from the claimed invention. In particular, Ecker *et al.* teach that RNase H is an endonuclease that cleaves the RNA strand of RNA:DNA duplexes and that activation of this enzyme by an antisense ***DNA*** oligonucleotide results in cleavage of the RNA target (column 4, lines 37-41). Accordingly, Ecker *et al.* teach that preferred antisense oligonucleotides are ***DNA oligonucleotides,*** *e.g.*, having phosphodiester or phosphorothioate inernucleoside linkages, since they activate the cleavage of target RNA by RNase H and thereby "greatly enhance the ability of antisense oligonucleotides to inhibit target RNA expression" (column 4, lines 28-42). Accordingly, one would not have been motivated nor have had a reasonable expectation of success, based on the teachings of Ecker *et al.*, to substitute the antisense DNA oligonucleotides of Ecker *et al.* with an siRNA, since Ecker *et al.* teach that DNA oligonucleotides are preferred for inhibition of target RNA expression.

The teachings of Hammond *et al.* and Bass *et al.* fail to make up for the deficiencies of Ecker *et al.* Both the Hammond and Bass references merely teach that RNAi is more "robust" than antisense technologies. Both the Hammond and Bass references fail to teach or suggest siRNAs comprising <u>any</u> modified nucleotides, let alone ***modified nucleotides positioned opposite point mutations*** in mutant alleles, nor do these references teach that such modified siRNAs may be used to achieve ***single nucleotide discrimination*** between a wild type and mutant allele or ***direct allele-specific cleavage*** of mRNA encoded by a mutant allele, as required by the claims.

Tuschl *et al.* also fails to make up for the deficiencies of Ecker *et al.* Tuschl *et al.* teach that siRNA molecules are useful for mediating RNA interference. Tuschl *et al.* disclose that the ***stability of siRNAs against degradation*** may be enhanced by the "substitution of pyrimidine nucleotides by modified analogues" including nucleobase-modified ribonucleotides, such as "uridines or cytidines modified at the 5-position, *e.g.*, ... 5-bromo uridine" and that these modifications "may be located at positions that do not interfere with RNAi mediating activity." Thus, Tuschl *et al.* fail to teach or suggest the incorporation of a modified base into an siRNA for any purpose other than to ***increase stability*** against degradation. As set forth in Applicant's previous Response filed February 15, 2007, Tuschl *et al.* fail to teach both the ***structure*** and the ***function*** imparted by that structure of the presently claimed siRNAs. In particular, Tuschl *et al.* fail to teach or suggest the specific ***positioning of a modified base in the antisense strand of an siRNA opposite a point mutation in the target mRNA*** of a mutant allele, let alone that such

siRNAs can be used for ***single nucleotide discrimination*** between a wild type and mutant allele or to ***direct allele-specific cleavage*** of mRNA encoded by a mutant allele, as required by the pending claims.

The teachings of Hojo *et al.* also fail to make up for the deficiencies of Ecker *et al.* Hojo *et al.* merely teach that pulmonary fibrosis is associated with overexpression of p53, and that such p53 overexpression is often associated with G: C to A:T and A:T to G:C transitions. Hojo *et al.* is devoid of any teaching regarding the use of siRNAs, or any other molecule, to direct the cleavage of a mutant gene (*e.g.*, mutant p53 as described by Hojo et al.), let alone siRNAs comprising a ***modified nucleotide positioned opposite the specific point mutations in a mutant allele***, as presently claimed. Hojo *et al.* fail to teach or suggest an siRNA capable of single nucleotide discrimination, wherein the antisense strand comprises ***5-bromo-uridine or 5-iodo-uridine positioned opposite a point mutation of adenine*** in a mutant allele, as required by claim 6, or comprises ***2,6-diaminopurine positioned opposite a point mutation of thymine*** in a mutant allele, as required by claim 8.

In view of the foregoing, one skilled in the art would not have been motivated to combine the teachings of the cited art to arrive at the present invention. There is nothing in the teachings of Ecker *et al.*, Hojo *et al,* Hammond *et al.*, Bass *et al.* or Tuschl *et al.* that would motivate one of ordinary skill in the art to combine the cited prior art references, let alone to combine them in such a way as to arrive at the claimed invention.

Moreover, even if the motivation to extend the teachings of Ecker *et al.* to an RNAi-based approach were to exist, (which it does not), the skilled artisan would have had no reasonable expectation of success in using the Ecker methodology. The skilled artisan would have readily understood, at the time the instant application was filed, that the results obtained for targeting an ***antisense molecule*** containing modified nucleotides to a mutated gene (as taught by Ecker *et al.*) cannot be extrapolated to the targeting of an ***siRNA molecule*** to a mutant allele (*e.g.*, wherein the siRNA comprises an antisense strand having a modified nucleotide positioned opposite the point mutation of the mutant allele) with any reasonable expectation of success because the molecules operate through very different cellular mechanisms. In particular, the state of the art at the time of filing recognized that an antisense oligonucleotide inhibits transcription and/or translation of target genes by base-pairing with the target sequence and blocking translocation of the transcription/translation machinery. In contrast, RNAi was recognized to involve the assembly of the RNA molecule with protein components to form a

nuclease complex, RNAi-Inducing Silencing Complex (RISC), that RISC utilizes an active mechanism to search for the homologous mRNA target and ultimately mediates degradation of the mRNA target. Given the distinct mechanism of RNAi as compared to that of antisense technology, the skilled artisan would not, based on the current state of the art and the teachings of the cited references, have had any reasonable expectation of success in making and using an siRNA as claimed.

In particular, one skilled in the art would have had no reasonable expectation that single-nucleotide discrimination between a wild type and mutant allele obtained with an ***antisense oligonucleotide,*** where the discrimination results solely from the presence of a single modified nucleotide positioned opposite a point mutation of the mutant gene, could be extrapolated to an ***siRNA*** having a single modified nucleotide similarly positioned opposite the point mutation of a mutant gene. This is because, as noted by the Examiner, and as evidenced by the Hammond *et al.* and Bass *et al.* references, RNAi is a ***remarkably efficient means of effecting gene silencing as compared to antisense technology***. As previously set forth in the Response filed October 2, 2008, at the time of filing of the instant application there were numerous reports that RNAi technology could tolerate single-base mismatches between the antisense strand of the siRNAs and the target RNA. Thus, one skilled in the art would not have had a reasonable expectation of success that any siRNA could be used to achieve single nucleotide discrimination. Indeed, there is nothing in Ecker *et al.* that teaches or even remotely suggests that a wild type gene would be ***resistant to RNAi.*** Ecker *et al.* merely teaches that the wild type ras gene, as compared to mutant ras, is resistant to the relatively inefficient ***antisense*** silencing technology of the reference. Notably, the siRNA methodology of the instant invention significantly silences a target mutant gene as compared to the corresponding wild type gene.

In the Office Action dated December 11, 2007, the Examiner states that "Applicant has not provided any evidence to the contrary supporting their conclusion that siRNA are incapable of allele specific silencing and are invited to do so." The Examiner points to Xu *et al.* as evidence that siRNAs are capable of allele specific gene silencing. In response, Applicants reiterate that whether single nucleotide specificity was achievable with RNAi technology had not been resolved by those skilled in the art at the time of the invention. For example, Boutla *et al.* (Boutla A et al., *Current Biology*, 11: 1776-80 (2001), previously made of record in the Information Disclosure Statement filed November 20, 2007), published prior to the priority date

of the application, indicated that single nucleotide discrimination was beyond the limits of siRNA technology. Boutla *et al.* reported that siRNAs differing from the sequence of their target mRNA at one or more nucleotides retained efficacy, indicating that the siRNA technology did not require perfect sequence complementarity of the siRNA with the mRNA to silence its expression. In an additional report published prior to the filing date of the application, Caplen *et al.* (Caplen NJ et al., *Hum. Mol. Genet.*, 11: 175-84 (2002), previously made of record in the Information Disclosure Statement filed November 20, 2007) attempted to selectively inhibit the expression of mutant huntingtin protein (which causes Huntingtin's Diease) with RNAi technology, but was unsuccessful. In view of the foregoing reports, one skilled in the art would have had no reasonable expectation that single-nucleotide discrimination would be successful. In fact, the skilled artisan would have expected that the wild-type allele would be silenced in addition to the mutant allele.

In summary, the Examiner has failed to point to any teaching in the Ecker *et al.*, Hojo *et al.*, Hammond *et al.*, Bass *et al.* and Tuschl *et al.* references that would compel one of ordinary skill in the art to make the claimed invention ***with any reasonable expectation of success***. The prior art must suggest "to those of ordinary skill in the art that they ***should*** make the claimed composition or device, or carry out the claimed process" and [b]oth the suggestion and the ***reasonable expectation of success*** must be founded ***in the prior art, not in the applicant's disclosure*** (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). In view of the foregoing, Applicants request that the rejection of the claims under § 103(a) be reconsidered and withdrawn.

Rejection of Claims 2-5, 7 and 9-17 under 35 USC § 103(a)

The Examiner has rejected claims 2-5, 7 and 9-17 under 35 U.S.C. §103(a) as being obvious over Ecker *et al.* (US Patent No. 5,965,722) in view of Hammond *et al.* (Nature Reviews Genetics 2001), Bass *et al.* (Nature 2001), Tuschl *et al.* (WO 02/44321) and Xu *et al.* (US 2004/0192629).

The Examiner relies on the primary reference, Ecker *et al.*, for the reasons set forth above. The Examiner acknowledges that Ecker *et al.* "do not teach siRNA targeted to a gene

correlated with a disease selected fro[m] ***ALS, Huntington's disease, Alzheimer'[s] disease or Parkinson's Disease***."

The Examiner further relies on Hammond *et al,* Bass *et al.*, and Tuschl *et al.* for the reasons set forth above. The Examiner further relies on Xu *et al.* for teaching that "allele-specific RNA interference of mutated genes comprises administering a siRNA targeted to the mutant gene," that "certain types of human disease, such as ALS, Hungtington's disease, Alzheimer'[s] disease or Parkinson's Disease are caused by dominant gain-of-function mutations" and that "it would be advantageous to selectively inhibit the mutated gene.""

The Examiner alleges that "Ecker *et al.* provide evidence that one of skill in the art would have had a reasonable expectation of inhibiting a mutant target gene" and "given that Tuschl *et al.* teach how to make and use any siRNA targeted to any gene, [and] Hammond *et al.* and Bass *et al.* teach siRNA are preferred over antisense compounds, one would have had a reasonable expectation of success at making a siRNA targeted to a mutated gene." The Examiner further alleges that "[o]ne of skill in the art would have had a reasonable expectation of success at targeting a gene responsible for disorders such as ALS given that Xu *et al.* teach a specific embodiment of selective targeting a mutant gene of ALS while not targeting the wild-type gene." The Examiner concludes that "the invention would have been prima facie obvious to one of skill in the art."

As set forth above, the teachings of Ecker *et al.* are directed to ***antisense DNA oligonucleotides*** comprising a modified nucleotide positioned opposite uracil of the mutated codon 12 of activated ras for the specific silencing of the mutant ras gene. Ecker *et al.* fail to teach or suggest ***any RNA oligonucleotide***, let alone an ***siRNA capable of single nucleotide discrimination***, wherein the antisense strand comprises a ***modified base positioned opposite at least one point mutation in a mutant allele***. Nothing in the teachings of Ecker *et al.* suggests a need in the art for an alternate molecule to an antisense molecule for the specific inhibition of expression of a mutant gene, let alone an siRNA. Thus, based on the teachings of Ecker *et al.*, one would not be motivated to seek alternate molecules to antisense for specific mutant gene silencing. Moreover, Ecker *et al.* ***teach away*** from the claimed invention. Ecker *et al.* teach that preferred antisense oligonucleotides are ***DNA oligonucleotides*** *(e.g.*, having phosphodiester or phosphorothioate inernucleoside linkages), since they activate the cleavage of target RNA by RNase H and "greatly enhance the ability of antisense oligonucleotides to inhibit target RNA expression." Accordingly, one would not have been motivated, based on the teachings of Ecker

et al., to substitute the antisense DNA oligonucleotides of Ecker *et al.* with an RNA oligonucleotide, since Ecker *et al.* teach that DNA oligonucleotides are preferred for inhibition of target RNA expression.

The teachings of Hammond *et al.*, Bass *et al.* and Tuschl *et al.* fail to make up for the deficiencies of Ecker *et al.* As set forth above, both the Hammond and Bass references fail to teach or suggest siRNAs comprising any modified nucleotides, let alone modified nucleotides positioned opposite point mutations in mutant alleles, nor do these references teach that such modified siRNAs may be used to achieve single nucleotide discrimination between a wild type and mutant allele. Also as discussed above, Tuschl *et al.* fail to teach or suggest an siRNA comprising a modified base for any purpose other than to ***increase stability against degradation***. In particular, Tuschl *et al.* fail to teach or suggest the specific ***positioning*** of a modified base in the antisense strand of an siRNA opposite a point mutation in the target mRNA of a mutant allele. Tuschl *et al.* also fail to teach or suggest that a modified base at ***any*** position in an siRNA can achieve ***single nucleotide discrimination*** between a wild type and mutant allele or to ***direct allele-specific cleavage*** of mRNA encoded by a mutant allele, as required by the pending claims.

Xu *et al.* also fails to make up for the deficiencies of Ecker *et al.* As discussed in Applicant's previous Response filed October 2, 2007, the Xu *et al.* priority document 60/423,507, filed November 4, 2002 (the only Xu *et al.* priority document which has a filing date preceding the priority date of the instant claims) fails to teach an ***siRNA comprising a modified base positioned opposite a point mutation in a mutant allele***, as required by the pending claims.

In view of the foregoing, one skilled in the art would not have been motivated to combine the teachings of the cited art to arrive at the present invention. There is nothing in the teachings of Ecker *et al.*, Xu *et al.*, Hammond *et al.*, Bass *et al.* or Tuschl *et al.* that would motivate one of ordinary skill in the art to combine the cited prior art references, let alone to combine them in such a way as to arrive at the claimed invention.

Moreover, as discussed above, even if the motivation to extend the teachings of Ecker *et al.* to an RNAi-based approach were to exist, (which it does not), the skilled artisan would have had no reasonable expectation of success in using the Ecker methodology. The skilled artisan would have readily understood, at the time the instant application was filed, that the results

obtained for targeting an ***antisense molecule*** containing modified nucleotides to a mutated gene (as taught by Ecker *et al.*) cannot be extrapolated to the targeting of an ***siRNA molecule*** to a mutant allele (*e.g.*, wherein the siRNA comprises an antisense strand having a modified nucleotide positioned opposite the point mutation of the mutant allele) with any reasonable expectation of success because the molecules operate through very different cellular mechanisms.

In particular, one skilled in the art would have had no reasonable expectation that single-nucleotide discrimination between a wild type and mutant allele obtained with an ***antisense oligonucleotide,*** where the discrimination results solely from the presence of a single modified nucleotide positioned opposite a point mutation of the mutant gene, could be extrapolated to an ***siRNA*** having a single modified nucleotide similarly positioned opposite the point mutation of a mutant gene. This is because, as noted by the Examiner, and as evidenced by the Hammond *et al.* and Bass *et al.* references, RNAi is a ***remarkably efficient means of effecting gene silencing as compared to antisense technology***. Indeed, at the time of filing of the instant application there were numerous reports that RNAi technology was so robust that it could tolerate single-base mismatches between the antisense strand of the siRNAs and the target RNA. Thus, one skilled in the art would not have had a reasonable expectation of success that any siRNA could achieve single nucleotide discrimination. Indeed, there is nothing in Ecker *et al.* that teaches or even remotely suggests that a wild type gene would be ***resistant to RNAi.*** Ecker *et al.* merely teaches that the wild type ras gene, as compared to mutant ras, is resistant to the relatively inefficient ***antisense*** silencing technology of the reference. Notably, the siRNA methodology of the instant invention significantly silences a target mutant gene as compared to the corresponding wild type gene.

In the Office Action dated December 11, 2007, the Examiner states that "Applicant has not provided any evidence to the contrary supporting their conclusion that siRNA are incapable of allele specific silencing and are invited to do so." The Examiner points to Xu *et al.* as evidence that siRNAs are capable of allele specific gene silencing. In response, Applicants reiterate that whether single nucleotide specificity was achievable with RNAi technology had not been resolved by those skilled in the art at the time of the invention. For example, Boutla *et al.* (Boutla A et al., *Current Biology*, 11: 1776-80 (2001)) published prior to the priority date of the

application indicated that single nucleotide discrimination was beyond the limits of siRNA technology. Boutla *et al.* reported that siRNAs differing from the sequence of their target mRNA at one or more nucleotides retained efficacy, indicating that the siRNA technology did not require perfect sequence complementarity of the siRNA with the mRNA to silence its expression. In an additional report published prior to the filing date of the application, Caplen *et al.* (Caplen NJ et al., *Hum. Mol. Genet.,* 11: 175-84 (2002)) attempted to selectively inhibit the expression of mutant huntingtin protein (which causes Huntingtin's Diease) with RNAi technology, but was unsuccessful. In view of the foregoing, one skilled in the art would have had no reasonable expectation that single-nucleotide discrimination would be successful. In fact, the skilled artisan would have expected based on the foregoing reports that the wild-type allele would be silenced in addition to the mutant allele.

Moreover, Applicants submit that should the foregoing arguments not be found convincing by the Examiner, Applicants will consider filing a Declaration evidencing that the instant invention was made prior to Xu *et al.* (*i.e.*, priority document 60/423,507, filed November 4, 2002, the only Xu *et al.* priority document which has a filing date preceding the priority date of the instant claims) and, accordingly, that Xu *et al.* is not available as a prior art reference under § 103(a).

In summary, the Examiner has failed to point to any teaching in the Ecker *et al.*, Hammond *et al.*, Xu *et al.*, Bass *et al.* and Tuschl *et al.* references that would compel one of ordinary skill in the art to make the claimed invention. The prior art must suggest "to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process" and [b]oth the suggestion and the ***reasonable expectation of success*** must be founded ***in the prior art, not in the applicant's disclosure*** (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

In view of the foregoing, Applicants request that the rejection of the claims under § 103(a) be reconsidered and withdrawn.

In view of the above amendments and remarks, it is believed that this application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Dated: January 12, 2009

Respectfully submitted,

By _____
Jill A. Mello
Registration No. 55,450
For
Debra J. Milasincic
Registration No.: 46,931
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicant